Participant Information Sheet

Targeting beta-cell function to achieve remission of type 2 diabetes (REACTIVATE) – Phase 2

Chief Investigator

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Targeting beta-cell function to achieve remission of type 2 diabetes

We would like to invite you to take part in a research study. Before you decide, it is important that you understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish.

- **Part 1 tells you the purpose of this study and what will happen if you take part.**
- **Part 2 gives you more detailed information about the conduct of the study.**

Ask us if there is anything that is not clear or if you would like more information. Take your time to decide whether or not you wish to take part.

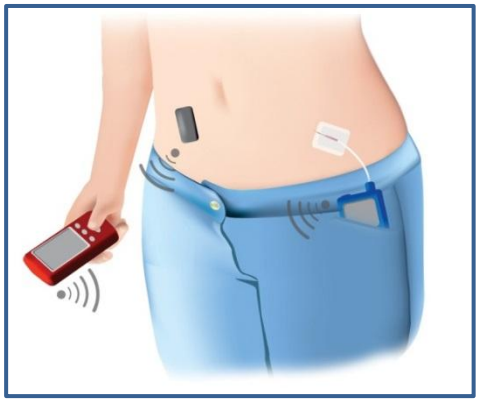
Part 1

Introduction

Recently it has been shown that it is possible to reverse type 2 diabetes and achieve remission, which is when blood glucose levels are below the diabetes range without the need for any diabetes medications. Treatments that can put type 2 diabetes into remission include low-calorie meal replacement diets which can be difficult to follow, and weight-loss surgery which many people find too extreme.

A healthy pancreas releases insulin according to the body's needs to keep blood glucose levels within a narrow range. In type 2 diabetes the pancreas is unable to produce enough insulin. Research studies have shown that insulin treatment soon after diagnosis can improve glucose levels and help the insulin-producing cells in the pancreas to recover and put type 2 diabetes into remission.

This study will find out if using a new diabetes technology (closed-loop system), which automatically gives insulin to keep glucose levels in target, can allow the cells in the pancreas that usually make insulin to rest for a short period, so people can make more of their own insulin in the long-term and achieve remission of their diabetes. The closed-loop system includes a small glucose sensor worn on the arm, an insulin pump which continuously gives insulin through a very thin tube inserted under the skin which is changed every 2-3 days and a computer algorithm on a smartphone that calculates the correct insulin dose based on the sensor readings.



The closed-loop system used in this study for 3 months is called CamAPS HX, which is approved for use in people with type 2 diabetes. It comprises: (1) Freestyle Libre 3 glucose sensor (Abbott Diabetes Care, CA, USA), (2) YpsoPump insulin pump (Ypsomed, Switzerland) that delivers the insulin and (3) CamAPS HX App (CamDiab, UK) on a smartphone which communicates with the insulin pump and the glucose sensor.

What is the purpose of the study?

The purpose of this study is to find out if the closed-loop system can allow the cells in the pancreas that usually make insulin to rest for a short period, so people can make more of their own insulin in the long-term and achieve remission of their type 2 diabetes. The closed-loop system will be compared to usual diabetes medications to see which treatment can help more people get remission of their type 2 diabetes after 12 months.

Why have I been invited?

You have been invited because you have type 2 diabetes diagnosed between 6 months and 5 years ago, and an HbA1c >48mmol/mol (6.5%) and have been taking medication to manage your diabetes for at least 3 months. We aim to include 56 adults in the study.

Do I have to take part in this research?

No. It is up to you to decide whether or not to take part. If you do, you will be given more detailed information and will be asked to sign a consent form. You are still free to withdraw at any time and without giving any reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?

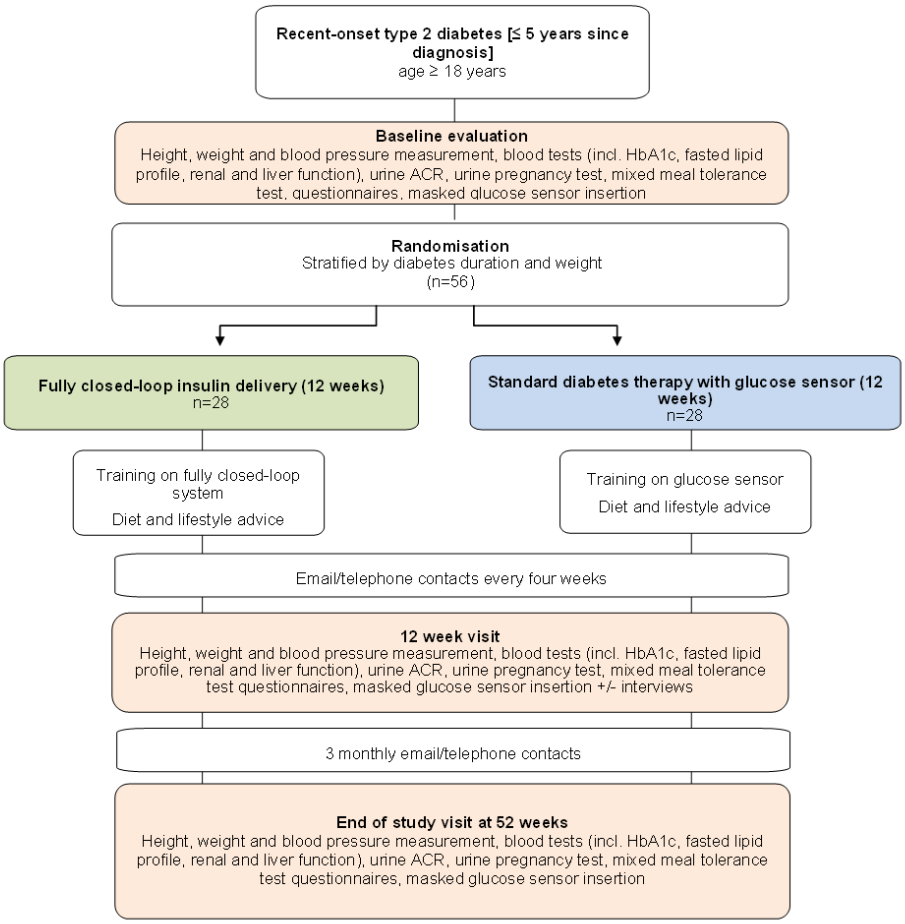
The study consists of up to 5 visits which will take place at the Clinical Research Centre. The total study duration is just over 12 months. The following sections describe what happens at each of the study visits in detail.

Visit 1 - Recruitment visit

Once you have had enough time to read this information sheet, if you would like to hear more about the study or would like to participate, you will be invited to attend the recruitment visit.

You will be provided with detailed information about the study and any questions you have will be answered. If you decide to participate, you will be asked to sign a consent form. At the visit, the following will be done:

- Height, weight and blood pressure measurement
- Demographics, medical and diabetes history, and medications recorded.
- Blood tests including HbA1c, liver and kidney function, lipids, gut and pancreas hormones. DNA analysis will also be undertaken on blood samples provided.
- Urine test to measure urine protein levels and a urine pregnancy test will be done for all females of childbearing age. If you are pregnant at the visit you will not be able to take any further part in the study.
- Mixed meal test to find out how much insulin your own pancreas makes. It involves drinking a milkshake and then taking blood samples from a cannula for 2 hours afterwards.
- A masked glucose sensor inserted and worn for the next 2 weeks (you will not be able to see your glucose levels) while you continue with your usual diabetes medications. If you are already using a glucose sensor, you can keep using this too.
- Complete questionnaires



Visit 2 – Randomisation visit

Two weeks after the recruitment visit you will be invited to Visit 2. This visit can be done remotely if preferred or can be combined with Visit 3. We will review the data from the masked glucose sensor to make sure that enough data has been recorded. A minimum of 10 days of data are needed for you to be able to start the study. Randomisation to decide which of the two groups you will be in will be done at this visit. You will either be randomised to use the closed loop system (**closed-loop group**) for the next 12 weeks or to continue with your current diabetes medications and use a glucose sensor for the next 12 weeks (**control group**). The group you are allocated to is a chance selection (like the toss of a coin) by a computer programme. The research team have no control over this decision.

Visit 3 - Training and initiation of the study devices

You will be invited to attend the Clinical Research Centre. This visit includes training on the study devices to ensure safe and effective use. This visit can be combined with Visit 2 if you and the study team feel this is appropriate.

Everyone in the study will receive diet and lifestyle advice from a diabetes educator at this visit to help you to achieve remission of your diabetes.

Closed-loop group:

You will be shown how to use the study glucose sensor, insulin pump and the closed-loop system, including how to manage high and low glucose levels (hyper- and hypoglycaemia). You will be provided with all the study devices including a smartphone with the closed-loop App if required. The session will be led by a diabetes educator or member of the study team and you will also be provided with easy-to-follow user guides for the closed-loop system. Your ability to use the closed-loop system will be assessed by the study team. You need to be able to show safe use of the system to continue with the home study phase. You will start using the system once the training is completed.

You will be asked to stop all your other diabetes medications for the next 12 weeks. You will be able to drive while following the standard precautions and regulations. We advise you to inform your insurance company of your involvement in the study. You do not need to inform the DVLA. A telephone helpline will be available to support you with any problems using the closed-loop system.

Control group - standard insulin therapy and glucose sensor:

You will be shown how to use the glucose sensor and how to review your glucose patterns. The session will be conducted by a diabetes educator or member of the study team and you will be provided with an easy-to-follow user guide for the glucose sensor. Your ability to use

the glucose sensor will be assessed by the study team. You need to be able to show safe use of the glucose sensor to continue with the home study phase. You will be asked to continue with your usual diabetes medications and wear the glucose sensor for the next 12 weeks. A telephone helpline will be available to support you with any problems using the glucose sensor.

Study contacts during treatment period

You will be contacted by email/telephone within 48 hours and at 1, 4 and 8 weeks after the training visit. These contacts are to look at your glucose data and to record any medical or device issues, or changes in medication or other medical conditions.

Visit 4 – 3 month visit

Three months after visit 3 you will be asked to attend the Clinical Research Centre where the following will be done:

- Height, weight and blood pressure measurement
- Blood tests including HbA1c, liver and kidney function, lipids, gut and pancreas hormones. DNA analysis will also be undertaken on blood samples provided.
- Urine test to measure urine protein levels.
- Mixed meal test
- A masked glucose sensor inserted and worn for the next 2 weeks.
- Complete questionnaires.

At this visit you will return the study devices and the study team will decide whether to adjust your diabetes medications depending on your HbA1c.

Study contacts after treatment period

You will be contacted by email/telephone 3 and 6 months after visit 4. We will ask you to do a blood test for HbA1c which you can do at home. These contacts are to look at your glucose data and to decide whether to increase or reduce your diabetes medications. We will also record any medical issues, or changes in medication or other medical conditions.

Visit 5 – End of study visit

Nine months after visit 4 you will be invited to attend the Clinical Research Centre where the following will be done:

- Height, weight and blood pressure measurement

- Blood tests measuring HbA1c, liver and kidney function, lipids, gut and pancreas hormones. DNA analysis will also be undertaken on blood samples provided.
- Urine test to measure urine protein levels.
- Mixed meal test
- A masked glucose sensor inserted and worn for the next 2 weeks.
- Complete questionnaires.

After this visit your diabetes care will be managed by your usual diabetes team (GP surgery or hospital diabetes team).

Interviews

Some participants in the closed-loop group will be asked to take part in an interview at the end of the closed-loop period. The interview will be conducted by an experienced researcher who understands diabetes. These interviews will be confidential and will allow you to talk openly and honestly about your diabetes self-management, your motivation to achieve remission of your diabetes and your experiences of the technology and the trial. Interviews may be both audio and video recorded. The interview files are encrypted as they are recorded, password protected and uploaded to a secure file store only accessible to the research team. Recordings are not kept long-term on the recording device. Recording files may be transferred securely to a third party trusted professional service for transcription. Direct quotes from the interview may be published but would be anonymised.

Will I be reimbursed?

As an appreciation of your time and effort you will receive £100 for completing the study. In addition, all reasonable travelling expenses will be reimbursed. Reimbursement will be paid either by bank transfer (if you are willing to provide your bank details) or vouchers from the research team's organisation.

What are the possible risks of taking part?

During this study, you may experience a hypo (low glucose level) similar to the ones that may happen in everyday life with diabetes. We will ask you to treat it in the same way you normally treat a hypo. There is a risk of hyperglycaemia (high glucose), especially after the mixed meal test, which is similar to the risk that a person with type 2 diabetes experiences on a daily basis. We aim to minimise these risks by providing you with education about managing hypo- and hyperglycaemia. We will spend time helping you to set the alarms on the devices so that you are warned in advance about any hypos or if your blood glucose rises too high in the first 12 weeks.

When a cannula is inserted and blood samples are taken for the study, some bruising or minor discomfort may also occur at the site. You will have to attach the small glucose sensor to your upper arm every 14 days. Some bruising, itchiness, redness or bleeding at the site of sensor insertion may occur. Inserting the sensor has a low risk of developing a local skin infection. Insulin pump therapy (if in the closed-loop group) can cause slight discomfort or bruising at the time of insertion of the cannula.

In some people who already have eye problems related to diabetes (retinopathy), improving glucose levels very quickly can initially make this worse. This only happens rarely, and in the longer-term good glucose control reduces the risk of eye problems progressing. We will ask you to make sure you attend your usual eye screening appointments, to ensure any changes are picked up early.

What are the possible benefits of taking part?

We cannot guarantee that taking part in this study will benefit you. You will receive diet and lifestyle advice from a diabetes educator and have frequent contact with the study team which may help with your diabetes self-management. The information provided by the glucose sensor and/or closed-loop system can be used to optimise your usual diabetes treatment and this may have benefits. Taking part in this study could also help in further development of closed-loop systems that can help more people with type 2 diabetes to achieve remission.

Who should I talk to if I have any questions or concerns?

If you have any questions regarding this study, please contact the following person:

Principal Investigator: Dr Charlotte Boughton
University of Cambridge
Level 4, Institute of Metabolic Science
Box 289, Addenbrooke's Hospital, Hills Rd
Cambridge CB2 0QQ

Email: cb2000@medschl.cam.ac.uk
Tel: +44 (0) 1223 769 066

On behalf of the Study Team, we would like to thank you for taking the time to consider participating in this important research study.

This completes part 1 of the Information Sheet.

If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.

Part 2

What if relevant new information becomes available?

You will be informed as soon as possible if any new information becomes available during the course of the study that may affect your willingness to participate in the study. If you decide not to continue, the study doctor will arrange for your usual care to continue.

What will happen if I don't want to carry on with the study?

If you decide not to participate in this study, it will not affect your future treatment in any way. If you agree to take part, you are free to withdraw at any time without explanation. If you withdraw from the study we will use the data collected up to your withdrawal.

What if there is a problem?

Any complaint about the way you have been dealt with during the research study or any possible harm you might suffer will be addressed. If you have a concern about any aspect of this study, please ask to speak to the researchers who will do their best to answer your questions (see contact details above). If you wish to complain or have any concerns about any aspect of the way you have been approached or treated during this research study, you can also do this through the NHS complaints procedure. In the first instance it may be helpful to contact Addenbrooke's Patient Advice and Liaison Service (PALS). You can contact PALS by calling 01223 216 756 or by email: pals@addenbrookes.nhs.uk at your hospital.

In the event that something does go wrong and you are harmed by taking part in the research that is due to someone's negligence then you may have grounds for a legal action for compensation against Cambridge University Hospitals NHS Foundation Trust or the University of Cambridge. The normal National Health Service complaints mechanisms will still be available to you (if appropriate). The University has obtained insurance which provides no-fault compensation i.e. for non-negligent harm; you may be entitled to make a claim for this.

Will my GP be informed?

We will inform your GP of your participation in this study after you have consented to this.

How will we use information about you?

Cambridge University Hospitals NHS Foundation Trust (CUH) and the University of Cambridge are the joint Sponsors for this research study. They will need to use information from you and your medical records for this research study. Cambridge University Hospitals NHS Foundation Trust will collect your name, NHS number and contact details to contact you about this study, to do the research and to check your records to make sure that the research is being done properly. Information about you might be securely transferred between the

research team at different research sites in relation to your participation in this research. If you do not have a hospital medical record with Cambridge University Hospitals we will ask your GP to confirm your medical record. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. We will keep all information about you safe and secure.

Once we have finished the trial, we will keep some of the data so we can check the results. Cambridge University Hospitals will keep identifiable information about you from this study for 5 years after the trial has finished and will be disposed of securely thereafter. We will write our reports in a way that no-one can work out that you took part in the trial.

De-identified information about your health and care relevant to this research may be made available to other organisations. These organisations may be NHS or other public sector organisations, academic institutions, charities and commercial companies in the UK or abroad. Before your data is shared with other organisations all personal identifiers, such as names, addresses and dates of birth, will be removed. Making information from trials available for further research helps maximise the benefit of conducting trials and allows other researchers to verify results and avoid duplicating research. To facilitate this, some trial datasets are made available to researchers via a public online database and become “open data”. Data are thoroughly de-identified before they are submitted to an open data platform and once the data are uploaded, we do not have control over how they are used.

What are your choices about how your information is used?

You can change or stop your participation in this research study at any time, without giving a reason, but we will keep information about you that we have already collected. We need to manage your records in specific ways for the research to be reliable. This means that we will not be able to let you see or change the data we hold about you.

Where can you find out more about how your information is used?

You can find out more about how we use your information:

- at www.hra.nhs.uk/information-about-participants/
- for Cambridge University Hospitals NHS Foundation Trust, please visit: https://www.cuh.nhs.uk/participant-privacy/ or email the Data Protection Officer at: cuh.gdpr@nhs.net
- for University of Cambridge, please visit: https://www.information-compliance.admin.cam.ac.uk/data-protection/medical-research-participant-data, or email the Information Governance team at: researchgovernance@medschl.cam.ac.uk.

What will happen to any samples I give?

Blood samples collected during the research will either be analysed immediately and disposed of or will be labelled with your study identification number, stored securely in a freezer in the local Clinical Research Centre and disposed of securely after being analysed in the Cambridge University Hospitals Laboratory. Urine samples collected during this study will be analysed immediately and disposed of after analysis.

What will happen to the data collected?

Once the study is finished all data will be entered onto a computer and will be used to analyse the results. These study results may be presented at scientific meetings or published in a scientific journal. In addition, fully anonymised data may be shared with researchers and collaborating partners in USA and Europe, or commercial companies for the purpose of advancing the management and treatment of diabetes.

Who is organising and funding the research?

The research study has been funded by an EFSD / Novo Nordisk Foundation Future Leaders Award. Professor Roman Hovorka, who is an Investigator for this study, is also Director of CamDiab, the company which makes the closed-loop app. The joint sponsors of the study are the Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge.

Who has reviewed the study?

Before any research goes ahead it has to be checked by an Ethics Committee. This project has been reviewed by the East of England - Cambridgeshire and Hertfordshire Research Ethics Committee Research Ethics Committee.

If I agree to join the study

The study will be explained to you in more detail during the recruitment visit. During this visit you will be able to ask questions and voice any queries. Once you have agreed to take part, we will ask you to sign a consent form.

What will happen at the end of the study?

At the end of the study your diabetes care will be managed by your usual diabetes team (GP surgery or hospital diabetes team). A summary of the results of the study will be available on the University of Cambridge departmental website.

This completes part 2 of the Information Sheet.

Thank you for your time and interest in our research.